REMARKS

The specification has been amended to reflect the national stage status.

The "use" claims have been cancelled without prejudice. The subject matter of claim 16 is covered by pending claim 14. The subject matter of claim 17 has been rewritten in U.S. format and presented as new claim 18.

Minor typographical errors have been corrected in the specification which are self-explanatory.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached pages are captioned "**Version with markings to show changes made**".

Favorable action on the merits is solicited.

Respectfully submitted,

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January 18, 2002

AGENT FOR PREVENTING RECURRENCE OF CEREBROVASCULAR DISORDER AND AGENT FOR AMELIORATING TROUBLES FOLLOWING CEREBROVASCULAR DISORDER AND INHIBITING PROGRESS THEREOF

This application is a 371 of PCT/JP00/04830 filed July 19, 2000.

Technical Field

The present invention relates to an agent for preventing recurrence of cerebrovascular disorder comprising a compound having an angiotensin II antagonistic activity, a prodrug thereof or a salt thereof as an active ingredient, as well as an agent for ameliorating troubles following cerebrovascular disorder and inhibiting progress thereof comprising a compound having an angiotensin II antagonistic activity, a prodrug thereof or a salt thereof as an active ingredient.

Background Art

According to the classification of cerebrovascular disorder, 3rd edition (MINDS-III, Stroke 21:637-676, 1990), National Institute of Neurological Disorders and Stroke (MINDS), cerebrovascular disorder is classified into asymptomatic cerebral infarction, transient ischemic attack (TIA), cerebral apoplexy, cerebrovascular dementia, and hypertensive encephalopathy. The type of cerebral apoplexy includes cerebral hemorrhage, subarachnoid hemorrhage, cranial hemorrhage accompanying a malformation in cerebral

1 capsule	200 mg

(1), (2), (3) and 1/2 of (4) are mixed, kneaded and granulated. The remainder of (4) is added thereto, and the whole is encapsulated in a gelatin capsule.

Example 2. Tablets

(1) Candesartan cilexetil	30 mg
(2) Lactose	35 mg
(3) Corn starch	150 mg
(4) Crystalline cellulose	30 mg
(5) Magnesium stearate	5 mg
1 tablet	250 mg

(1), (2), (3), 2/3 of (4) and 1/2 of (5) are mixed, kneaded and granulated. The remainders of (4) and (5) are added to the granules which are then molded into a table by compression.

Experimental Example 1

Action of Candesartan cilexetil in ameliorating troubles following cerebrovascular disorder in ~~spontaneous hypertension rat with ease spontaneous cerebral apoplexy~~ Stroke-Prone Spontaneously Hypertensive Rat (SHRSP)

Method:

Male SHRSP are used. SHRSP are separately raised and given 1 % saline solution as drinking water to promote and regulate occurrence of cerebral apoplexy. To regulate apoplexy symptoms, rats expressing the non-voluntary

motility of raising the foreleg are divided one after another into a control group and a drug administration group. After the first fit, the drinking water is replaced by tap water, and then nerve symptoms are observed. During observation, the rats are examined for severity of nerve symptoms and for change in their weight. After the final administration, the rats are allowed to bleed to death under anesthesia and subjected to histological investigation.

Industrial Applicability

The renin-angiotensin system is revealed to play an important role in the progress of cerebrovascular lesions accompanying hypertension. Then, a compound having an AII antagonistic activity (particularly Candesartan cilexetil) can be expected to ~~inhibit the progress of lesions (carotid artery lesions) responsible for cerebral arteriosclerosis and ischemic~~ inhibit Cerebral arteriosclerosis and the progress of arteriosclerotic lesions (for example, Carotid artery lesions) responsible for ischemic cerebrovascular disorder not only by the vasodilator action but also by the action of improving endothelial cell functions and inhibiting inner membrane thickening (correction of vascular remodeling). Further, reduction in cerebral blood flow and microcirculation in brain are ameliorated by the action of ameliorating the ability for automatic circulation of cerebral circulation, and there are further brought about various actions for

protection of brain (nerves), correction of an abnormality in fibrinolytic system, amelioration of blood properties, etc. Thus, the compound is useful for preventing recurrence of cerebrovascular disorder or for ameliorating troubles following cerebrovascular disorder and inhibiting progress thereof.

That is, Candesartan cilexetil having the following actions can be used effectively as an agent for preventing recurrence of cerebrovascular disorder or as an agent for ameliorating troubles following cerebrovascular disorder and inhibiting progress thereof.

(1) Long-lasting action of reducing blood pressure without adversely influencing cerebral blood flow

It is reported that Candesartan, i.e. an active metabolite of Candesartan cilexetil, can deviate the lower limit of automatic regulation leftward (toward lower blood pressure level) (Vraamark T et al., J Hypertens 13:755-761, 1995), and in a patient with cerebrovascular disorder where the ability for automatic regulation of cerebral vessels is hindered, the recurrence of cerebrovascular disorder can be prevented by preventing or decreasing cerebral ischemia by the mechanism of blood flow kinetics as a cause of the recurrence. Further, Candesartan cilexetil can prevent recurrence of cerebrovascular disorder by its stable blood pressure depressing action through 24 hours, thus stably

controlling blood pressure whereby a significant reduction in blood pressure at night or an increase in blood pressure from night to early morning or in early morning, which is a cause of occurrence and recurrence of cerebrovascular disorder, is prevented. Further, Candesartan cilexetil can lower blood pressure safely to a therapeutically desired level in a patient with cerebrovascular disorder having various complications such as diabetes, cardiac diseases and renal diseases in addition to hypertension, thus significantly contributing to inhibition of the progress of organ disorders due to these complications without causing significant reduction in blood pressure, and finally the recurrence of cerebrovascular disorder can be prevented by reducing the dangerous factors for recurrence of cerebrovascular disorder.

(2) Anti-arteriosclerosis action:

It has been revealed that AII have not only a strong vasoconstricting action but also various actions such as proliferating action, inflammation action, oxidizing action, vascular penetrating action, etc., thus playing an important role in the progress of not only hypertension but also cerebrovascular lesions. That is, it is reported that AII ~~thickens~~ induces hypertrophy of cells via expression of oncogenes and growth factors, thickens vascular walls by an increase in production of extracellular substrate, activates a

transcriptional factor (NF-κB) to increase expression of a monocyte chemotactic factor (Hernandez-Presa M, et al., Circulation 95, 1532-1541, 1997), and induces production of free radicals from inflammatory cells (Zafari AM, et al., Hypertension 32, 488-495, 1998), thus significantly influencing various organ disorders including cerebrovascular disorder. Candesartan cilexetil not only inhibits these disorders attributable to AII thereby treating hypertension but also exerts actions for prevention of progress of arteriosclerosis, amelioration of vessel remodeling, amelioration of microcirculation, inhibition of edema, amelioration of endothelial cell functions (promotion of NO production in endothelial cells), and protection of cells thereby preventing the progress and recurrence of cerebrovascular disorder and ameliorating troubles after cerebrovascular disorder.

(3) Reduction in dangerous factors for diabetes etc.:

Candesartan cilexetil is known to improve insulin sensitivity clinically (Iimura O., et al., Am J Hypertens 8, 353-357, 1995), and can ameliorate various disorders accompanying an abnormality in ~~sugar resistance~~ glucose tolerance, diabetes and a reduction in insulin sensitivity as dangerous factors for recurrence of cerebrovascular disorder thereby preventing the progress and recurrence of cerebrovascular disorder and ameliorating troubles after cerebrovascular

disorder.

(4) Brain-protecting action:

Candesartan cilexetil has actions for anti-inflammation, anti-oxidization, anti-edema, amelioration of microcirculation and improvement of endothelial cell functions as described in the above (2), and can inhibit vasoconstriction and promotion of platelet agglutination caused by various ~~vascular agonists~~ vasoconstrictor such as ~~endoserin~~ endothelin and thromboxane induced and enhanced by AII, whereby the penambra region can be saved by amelioration of blood flow and inhibition of cellular disorders at the acute stage of vascular infarction.

Further, it is reported that a disorder in the brain-blood barrier in an angiotensinogen knockout mouse is ameliorated by administration of an angiotensin peptide such as angiotensin IV (angiotensin 3-8) (Kakinuma Y. et al., Nat Med. 4, 1078-1080, 1998), and also that an angiotensin peptide such as AIV is related to memory and the action of increasing cerebral blood flow (Wright J W et al., Brain Res Rev 25, 96-124, 1997), and the increase in these peptides by administration of Candesartan cilexetil (decomposed products are increased by an increase in AII) can prevent the progress and recurrence of cerebrovascular disorder via the above-described actions and ameliorate troubles after cerebrovascular disorder.